

Emerging and re-emerging sexually transmitted diseases: A review of epidemiological evidences

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Abstract

Substantial increase in the outbreaks of sexually transmitted infections (STIs) and associated mortalities have raised international concerns. Concurrent with the escalation of established STIs, developing epidemics and outbreaks of newly emerging sexually transmissible pathogens pose serious problems for people and added burden and challenges for public health practitioners and researchers. Importantly, most of the emerging STIs are frequently found among vulnerable groups, such as men having sex with men and human immunodeficiency virus patients, which may result in large outbreaks in the near future. Furthermore, enhanced spread of antimicrobial resistance among these pathogens ever more limits treatment options for STIs. Thus, it is the optimal time to consider whether an infectious agent is sexually transmissible and develop treatment protocol for handling new STIs with pandemic potential. In this review, we explore emerging STIs, their current epidemiological status, and future perspective.

Key words: Antimicrobial resistance, emerging sexually transmitted infections, human immunodeficiency virus, men having sex with men group, re-emerging sexually transmitted infections, sexually transmitted infections

Introduction

Sexually transmitted infections (STIs) remain prevalent in the 21st century and constitute a health and economic burden globally. As a long-term goal, the WHO has endorsed the global STI strategy that targets to eliminate the STIs by 2030.^[1] Regrettably, more than 50% of new STI cases are found among adolescents, and 80% of the infections are widespread in developing countries which have limited resources. To this point, about 30 types of known infectious agents such as bacteria, viruses, fungi, parasites, and insects have been reported to cause STIs worldwide.^[2] The new infectious agents include diseases which are primarily transmitted by food, water, and vector but are now predicted to be disseminated through sexual contacts. These newly emerging STIs would be more dangerous than the typical STIs because of their unique methodologic and epidemiologic challenges for public health experts and research scientists.^[3,4] This puts forth the need for development of immediate action plans to anticipate, identify, and contain the emerging STIs which may become endemic and epidemics at the global level. This review has been envisaged to elicit the newly emerging STIs and their current epidemiological status. In

addition, we explored the challenges which lie ahead with respect to future perspective.

Newly Emerging Sexually Transmitted Infections

Increased international travel, unprecedented connectivity between people, and social networking have enhanced the dissemination of existing as well as newly emerging STIs at the global level. Due to these factors, and changes in sexual and behavioral practices, several diseases are found to be sexually transmitted or at risk to be so, which had previously been unknown. This includes *Shigella flexneri*, *Mycoplasma genitalium*, *Neisseria meningitidis*, methicillin-resistant *Staphylococcus aureus* (MRSA), hepatitis C, Ebola, Zika, and dengue [Table 1].^[3-5] In addition, as genital fluids are the major reservoir for microorganisms, they could disseminate from infected person to their partner through contacts. According to recent research, about 29 viral agents have been found from human semen.^[9] These pathogens are at a high risk of becoming STIs in the near future, whereas some of them are already recognized as sexually transmissible.

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Shigella flexneri

Shigella causes severe gastroenteritis called shigellosis, often causing bloody dysentery, especially in children in developing countries. Among the four *Shigella* species identified, *S. flexneri* is more important because of its higher mortality rate.^[10] The primary route of *Shigella* transmission is food and water resources which are either directly or indirectly contaminated with feces of an infected human. However, in the late 1970s, the sexual transmission of *S. flexneri* was found for the first time among men having sex with men (MSM) community, who were involved in anal and/or oral sex.^[11] At the end of the 20th century, this infection was frequently found among human immunodeficiency virus (HIV) patients as this may enhance the susceptibility or duration of the disease.^[12] Currently, *S. flexneri* is rapidly emerging as a STI in the MSM community, women, and children across the globe as per the epidemiological surveillances conducted in various countries. In addition, evolution of azithromycin and ciprofloxacin multidrug-resistant (MDR) *S. flexneri* strains poses a public health threat and has attracted the global level concerns. In the past 5 years, sexual transmission of MDR *S. flexneri* strains among MSM has increased exponentially in Europe, Australia, Asia, and North America.^[3] Thus, the case incidence of newly occurring *S. flexneri* and other species from this genus must be investigated carefully by clinicians and health-care experts to impede the potential of this species in emerging as a STIs.

Lymphogranuloma venereum

Lymphogranuloma venereum (LGV) is a chronic ulcerative, progressively destructive anogenital and systemic disease caused by the bacterium *Chlamydia trachomatis*. It is also responsible for causing several other STDs such as nongonococcal urethritis, cervicitis, pelvic inflammatory disease, and trachoma.^[12] The rectal involvement of LGV among MSM might cause colorectal strictures and fistulae if not treated properly. The first LGV infection among MSM was found in 1980 in the USA.^[13] The STI surveillance program launched in the UK reported about 2000 cases of LGV between 2003 and 2012. About 10,000 cases were reported from 15 countries between 2004 and 2016.^[14] In India, LGV cases were not predominant until the beginning of the 21st century.^[15] However, according to a recent study by Juyal *et al.*, LGV cases increased from 4.5% to 18.3% between 2011 and 2019, especially in patients attending a HIV clinic. Before these new outbreaks, LGV was predominant in heterosexual adults belonging to selected tropical and subtropical countries. Thus, sensitive LGV diagnostic assays must be included for rectal swabs and rectal biopsies of MSM patients who have participated in the receptive anal intercourses as an active approach for the diagnosis of anorectal chlamydia-like infection.^[16]

Entamoeba histolytica

Entamoeba histolytica, responsible for the amebic dysentery, is more common in the countries of the tropical region having poor hygienic circumstance.^[17] Primarily, this parasite spreads through the ingestion of water or food contaminated with feces containing cysts of *E. histolytica* and through fecal–oral transmission within household. Amebic colitis is a severe form of the disease which often causes bloody dysentery and febrile illness in some people. In the early 1980s, the sexual transmission of *E. histolytica* was noticed in MSM group who were involved in oral and anal sex.^[18] Since then, it is considered an

emerging STI. Several evidences, especially in the last decade, have exposed the signs of sexual transmissibility of *E. histolytica*. Studies conducted from various countries have revealed the increased prevalence of *E. histolytica* among MSM, HIV-negative, and HIV-positive groups. In addition, recent outbreaks have occurred in North America and certain Europe.^[19] Thus, *E. histolytica* has emerged as a major public health problem and has raised global level concerns.

Hepatitis A

Hepatitis A virus (HAV) causes an acute liver disease. Its primary mode of transmission is through anal/oral route.^[4] Evidence for sexual transmission of HAV was first found among MSM group in the USA during 1980. The prevalence of infection was about 30% in homosexuals, which was significantly higher than 12% of heterosexual group. Recently, large-scale outbreaks of HAV among MSM have been reported from various countries raising an alarm regarding their re-emergence, with a potential impact on high-risk sex network. Further, genotypic analysis has revealed the intercontinental dissemination of three HAV lineages among MSM group. About 1400 cases of HAV have been identified from June 2016 to May 2017 across 16 European countries.^[4] According to seroprevalence studies conducted in various Asian countries from 2000 to 2013, 15%–50% of HAV incidence was found in HIV-positive MSM people.^[20] Based on seroprevalence studies conducted in various parts such as Eastern India, Punjab, and Delhi, in India, high endemicity of HAV was found in MSM community.^[21]

Group B Streptococcus

Group B *Streptococcus* (GBS) is a significant cause of neonatal sepsis and meningitis in the people of low- and middle-income countries.^[22] This devastating pathogen generally inhabits the vagina and gut lumen of the healthy female. However, the problem arises when infected female is pregnant, which enhances the chance for developing invasive neonatal disease.^[23] Recent studies emphasize that the vaginal microbiome and STIs are interconnected. In a few cases of neonatal diseases, concurrent vaginal (mother) and urethral (father) colonization of GBS has been documented.^[24] Accordingly, several authors stated that GBS can be transmitted through sexual intercourses as higher colonization rate of GBS was detected from male urethra and sexually active adolescents attending STI clinics.^[25] On the contrary, certain researchers argue that sexual connections do not possibly seem to be the effective route of GBS circulation. However, frequent detection of GBS among people carrying STIs, especially prevalence of hypervirulent GBS strain ST17, needs to be considered seriously.^[26] Thus, further intensive studies are needed to authenticate the sexual transmission of GBS.

Neisseria meningitidis

N. meningitidis commonly colonizes the mucosal surface of the oropharynx. Its systemic spread leads to life-threatening meningitis and septicemia. The primary route of transmission happens via inhalation of respiratory droplets and contact with saliva from a carrier.^[27] There is an argument among the scientific community, whether *N. meningitidis* is a potential STI or not. Pieces of evidence suggest that the occurrence of *N. meningitidis* in the human urogenital tract could be the result of oral-genital sexual contact.^[6] Recently, invasive meningococcal disease outbreaks have occurred among MSM group members living in various continents, thereby raising more concerns toward this issue.^[28] Based on the study conducted by

Table 1. Key characteristics of emerging and re-emerging selected sexually transmitted infections.

Pathogens	Year of identification	Year of recognition as STI	Diagnosis method	Geography	Most vulnerable group	Clinical syndrome	Type of disease group	Primary mode of transmission	Whether associated with any co-infection?	Deadly?	Is vaccine available?
<i>Shigella flexneri</i>	1900.	First identified among MSM in 1974 in USA. ^[26]	Bacterial culturing and genome based detections	All over the world	Young children (Less than 5). People practising unsafe sexual activities, especially MSM.	Acute gastroenteritis. If untreated may lead to chronic colorectal fistulas and strictures	Extra genital	Food and water resources contaminate with feces from an infected person.	Yes. Infections are frequently seen in HIV infected patients.	No (Curable with antibiotics)	No
<i>Chlamydia trachomatis</i> (Lymphogranuloma venereum)	1833. ^[43]	First LGV infection found among MSM in USA in 1980. ^[43]	Genome based detection of genital lesions, rectal and lymph node specimens.	Spread all over the world. But, endemic in Africa, Asia, South America and Caribbean.	Can occur at any age but, predominant among sexually active population of the age group between 15 to 40.	Proctitis, proctocolitis, lymphadenopathy, strictures and fistulae	Genital and systemic	Transmits during un protected anal, vaginal and oral sex.	Yes. Significant association between HIV infected patients. In addition, increased risk of contracting hepatitis, syphilis etc.,	Yes. But rarely. (Curable with antibiotics such as doxycycline, erythromycin base or azithromycin)	No
Hepatitis A	1973.	Found among homosexual couples who attended sex clinic in USA in 1980.	Serological and genome based assays	Central and South America, Africa, Asia	Affects all age groups	Acute live disease, but seldom causes acute live failure	Extra genital	Food and water contaminated with the faecal and body fluids of an infected person	No	No (But, rarely fatal)	Yes
Group B Streptococcus (GBS)	1930.	Not widely recognised as STI	Bacteriological and genomic based analysis	All over the world	Pregnant women, neonates and elder people.	Neonatal sepsis, meningitis, miscarriage or stillbirth	Genital and gastrointestinal tract	Vertical transmission (either in utero or during passage through the neonatal GBS birth canal)	Yes. PLWHIV are at increased risk for not early but late-onset neonatal GBS disease.	Yes	Yes (GBS-MOPA Under clinical trial)
Entamoeba histolytica	Early 20 th century. ^[8]	Outbreak among MSM community in USA during 1960s.	Bacteriological and genomic based analysis	All over the world	All age group	Dysentery, liver abscess and cerebral amoebiasis	Extra genital	Ingestion of food or water contaminated with faeces of an infected person.	Yes. HIV is significantly associated with higher prevalence of <i>E. histolytica</i> infection.	Yes (Responsible for 1 million deaths per year)	Under clinical trials.
<i>Neisseria meningitidis</i>	1942.	Isolated from genitourinary tract of patients in USA in 1942	Bacteriological and genome based analysis	Observed worldwide	People who executes unsafe sex	Nonspecific urethritis and invasive meningococcal disease	Genital as well as systemic	Through unprotected sexual activities and nasal droplet from an infected person	Yes. Increased incidence of meningococcal disease among PLWHIV.	Yes (permanent disabilities such as brain damage, hearing loss, and learning disabilities also can happen)	Yes (Meningococcal conjugate and MenACWY)

Contd...

Table 1: Contd...

Pathogens	Year of identification	Year of recognition as STI	Diagnosis method	Geography	Most vulnerable group	Clinical syndrome	Type of disease	Primary mode of transmission	Whether associated with any co-infection?	Deadly?	Is vaccine available?
<i>Mycoplasma genitalium</i>	1981.	Detected among male patients with who attended sexual clinic in USA in 1981.	Genome based diagnosis	All over the world	People who executes unsafe sex	Non-gonococcal urethritis	Localized to reproductive parts	Through unprotected sexual activities	Yes. <i>M. genitalium</i> is positive association with HIV and Chlamydia trachomatis.	No (If left untreated may damage the immune system and make susceptible to other pathogens)	No
Hepatitis C	1974.	Found among homosexual couples who attended the county health department in USA in 1989.	Serological test	All over the world	All age groups	Cirrhosis and liver cancer	Systemic	Transmitted through blood and blood related products	Yes. Strong correlation between HIV and HCV.	Yes (But, 95% curable with antiviral drugs)	No
Methicillin-Resistant <i>Staphylococcus Aureus</i> (MRSA)	1961.	Detected in the 35 years old man who attended a sex clinic in USA in antibiotics 2007.	Bacteriological test with cefoxitin and oxacillin in antibiotics	All over the world	Elderly people especially the age of 60 and above	Pneumonia and Sepsis	Extra genital (Become systemic if untreated)	Skin to skin contact and sharing of infected things like cloths, equipments etc.,	Yes. HIV-infected people are at increased risks of acquiring MRSA	Yes, if untreated	No
Ebola virus	1976.	Detected in the heterosexual couple in Liberia in 2015.	Serological and genome based testing	Detected in more than 15 countries	All age groups	Ebola virus disease or Ebola haemorrhagic fever	Systemic	Close contact with body fluids of an infected person.	Unknown	Yes	rVSV-ZEBOV is under clinical trial.
Zika virus	1947.	Detected in the heterosexual couple in America in 2008.	Virological, serological and genome based testing	Spread over 86 countries	Pregnant women and infants	Congenital Zika syndrome	Systemic	Mosquito bite	Unknown	No (With lifelong morbidity)	No
Dengue virus	1789.	Reported in the MSM pair in Spain in 2019.	Virological, serological and genome based testing	Endemic in more than 100 countries	All age groups	Dengue virus infection and severe Dengue	Systemic	Mosquito bite	Unknown	Yes (if untreated)	Dengvaxia vaccine is available in some endemic countries.

Johnson *et al.*,^[29] *N. meningitidis* urethritis has increased from 2.78% in 2011 to 8.93% in 2015, especially in male patients. Both biochemical and high-throughput genomic studies have confirmed the existence of *N. meningitidis* among MSM community.^[30] These proofs authenticate the potential increase of sexually transmitted meningococcal urogenital infections.

Mycoplasma genitalium

M. genitalium causes nongonococcal urethritis in men. The Centers for Disease Control and Prevention has updated the STI guidelines very recently, in which *M. genitalium* has been highlighted as an emerging STI.^[31] It is estimated that more than 25% of nongonococcal urethritis is caused by *M. genitalium*. After the first case of *M. genitalium*-associated nongonococcal urethritis found in MSM during 1981, the influence of this bacterium in affecting the genital part has increased and reached their peak in recent times.^[32] A large study conducted among MSM group in Norway revealed 91 patients infected with *M. genitalium* out of 1778 samples screened.^[33] Furthermore, the ratio of *M. genitalium* infection is increasing over the years as compared to other STIs.^[34] The primary concerns about this bacterium have been both diagnosis and treatment. Nucleic acid amplification test is the only diagnostic tool available since it is challenging to cultivate at the laboratory. In addition, the growing antimicrobial resistance against azithromycin and moxifloxacin, there emerges an urgent need for effective control protocols.^[35] The availability of diagnostic facilities for *M. genitalium* among various sexual networks would identify more positive cases than we suspect as oral and anal sex has increased over the past decades.

Methicillin-resistant Staphylococcus aureus

The well-known hospital-acquired MRSA infection has also started spreading at the community level. Community-acquired MRSA is responsible for cutaneous and systemic infection, which is now not only predominant among a day-care center, sports teams, and military camp but also becoming prevalent in sexual communities such as sex workers and MSM groups. In the USA, a high prevalence of *S. aureus* was found among people visiting the STI clinic from October 2010 to April 2011.^[36] The high prevalence of MRSA was found among HIV-positive patients visiting the STI clinic at Atlanta in the USA between September 2007 and April 2008 indicating the emerging MRSA transmission in HIV community.^[37] Besides, several studies have reported the possible transmission of MRSA through oral sex as well.^[38,39] Apart from its STI-related manifestations, MRSA is a potential agent for causing infertility in both males and females. Hence, it is essential to be cognizant that sexually acquired MRSA is making his presence felt as a STI.

Ebola virus

Since its discovery in 1976, the largest outbreak happened in West Africa between 2014 and 2016, where more than 28,000 cases were reported, and over 11,000 deaths occurred.^[40] The transmission of fluids or skin contact from an infected person serves as a primary route of viral dissemination. Interestingly, the identification of Ebola's genomic material in the semen of the 2014–2016 Ebola epidemic's survivor raised the concern about the risk of their sexual transmission.^[41] The detection of Ebola infection in a woman who does not have symptomatic or recently diseased patients nearby indicated the possibility of other routes of transmission, especially through sexual contact. As expected, the patients' husband was an Ebola survivor,

and evidently, traces of virus were detected in his semen. Moreover, the high homology of Ebola's RNA sequence between this couple authenticated the sexual transmission of this virus.^[42,43] Hence, initial reports indicate the possibility of the emergence of Ebola as one of the established causes of STI in future.

Zika virus

The first large outbreak of Zika occurred in French Polynesia during 2013, followed by a second outbreak in Brazil.^[7] This infection leads to microcephaly and other congenital abnormalities in the developing fetus and infants. *Aedes aegypti* and *Aedes albopictus* are the two crucial mosquito species that predominantly transmit Zika virus.^[44] The detection of this virus in the testis, male genital tract, and semen made the possibility of their sexual transmission.^[45]

Although the earlier studies predicted the traces of Zika virus in human semen, live viral particles were recently detected in semen samples of infected people, which was mostly absent after 30 days of illness onset. This finding authenticated the possibility of sexual transmission of Zika virus from an infected person to their sexual partners. The first suspected case of sexual transmission happened in America during 2008, followed by the second recorded case from French Polynesia in 2013. Currently, the sexual transmission of Zika has been reported at least from 13 countries, where the endemicity of the virus was not previously reported.^[46,47] Thus, to prevent the life-threatening difficulties associated with Zika virus, their sexual way of transmissions must be considered during management of the disease.

Dengue virus

Dengue is another vector-borne disease that is majorly disseminated by *A. aegypti* and *A. albopictus* mosquitoes. Several other routes of transmissions, including blood transfusion, organ transplantation, and breastfeeding, have been reported.^[48] In addition, detection of this virus in semen and vaginal fluids may find the way of their transmission through sexual intercourses from an infected person to an uninfected one.^[49,50] Although the traces of dengue virus have been detected in the genital secretions, their sexual transmissions are poorly reported. The first case of sexual transmission was reported from Spain in 2019. This case was confirmed by viral sequencing of samples collected from two males who recently had sex.^[51] Strains from both males were identical and matched to the currently circulating strain of Cuba, where only one among them visited the country in their entire lifetime. This confirms the sexual transmission of dengue virus and may pose significant public health importance soon. More epidemiological and genomic studies are needed before establishing dengue as a STI.

Challenges and Future Perspective

The mechanism of developing definitions and approaches to inspect the emerging sexually transmitted infectious agents for considering as an STI pathogen to be sexually transmissible must be developed. As per the assessment, the incidence of these STIs would continue to arise owing to enhanced human interconnectedness such as international travel and extensive use of social networks meant for sexual activities. Timely testing and treatment are mandatory at least for people from the vulnerable group like MSM and sexual workers. Special attention must be given to HIV patients as most of the emerging STIs are highly prevalent in this group. Thus, it is essential

to develop a robust surveillance system that comprises organism identification (both culture and genomic based) and treatment facilities at the primary health-care level for the newly emerging STIs.

The recent documentation of numerous viruses from semen made the obligation of investigating vaginal, anal, and even oral fluids of high-risk sexual network group by employing next-generation sequencing for the identification of pathogens with epidemic potential. This would help the health system to identify the possible emergence of these pathogens as STIs, which are commonly found in genitals. Evolving drug resistance in these emerging STIs raises public health concerns as it removes the possibility of curing diseases with available antibiotics. Lessons learned from “global HIV epidemics” is applicable to STI control as well, which encourage the significant cooperation among government, nongovernment, and private organization together with community contribution and engagement is crucial for the battle against emerging STI and related diseases.

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